REMARKS/ARGUMENTS

By this Amendment, claim 85 is canceled, claim 88 is amended, and claims 93-101 are added. Claims 5-6, 15, 17-25, 35-40, 46, 53, 57-68, 74, 87 have been withdrawn from consideration pursuant to a restriction requirement. Claims 1, 3-75, 80, 82-101 are pending.

Support for the amendments to the claims can be found throughout the Specification as filed, and specifically: support for the limitation in claims 93-95 for the limitation wherein the diagnostic or therapeutic moiety is separated from the PNA by a distance of from about 10A to about 30A by one or more spacer moieties can be found in ¶[0065]; support for the limitation in claims 96-98 for the limitation wherein the spacer moiety is hydrophilic can be found in ¶[0038]; support for the limitation in claims 99-101 wherein the compound comprises a branched dendrimer can be found in ¶[0035]. Cancellation of and/or amendment to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The cancellation and/or amendments to the claims are being made solely to expedite prosecution of the instant application.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

The Examiner's courtesy in granting an interview to Applicant and Applicants' representative on October 31, 2007 is gratefully acknowledged. Applicants' separate record of the substance of the interview is incorporated into the following remarks.

Double Patenting

The Examiner indicates that should claim 83 be found allowable, claim 85 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Without acquiescing to

the propriety of the Examiner's rejection, claim 85 has been canceled herein.

Rejection under 35 USC § 103(a)

Claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 86, and 88-92 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Tomalia et al. (US Patent No. 5,714,166), in view of both Meade et al. (US Patent No. 6,713,046) and Basu et al. This rejection is respectfully traversed.

The claims are patentable over the combination of the Tomalia et al. (US Patent No. 5,714,166), in view of both Meade et al. (US Patent No. 6,713,046) and Basu et al references for the following reasons. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). MPEP 2143. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention

does. (*KSR v Teleflex*, 12 S.Ct. 1727, 1740 (US 2007)).

The Examiner argues that Tomalia et al. teach all components necessary for this arrangement, and alleges that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property. The Examiner argues that the arrangement is not significant if it does not provide a novel feature, and that it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site, and that absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. The Examiner admits that Tomalia et al. does not teach a biodegradation cleavage site, but argues that Meade et al. teach a biodegradation cleavage site (Office Action at page 5). The Examiner argues that Tomalia et al. teaches a compound with the formula T-L1-P-L2-M, wherein M represents a PNA, T represents a targeting moiety that can bind a cell-surface molecule, P represents a dendrimer, and wherein M and T are associated with P via identical or different linkers, LI and L2 (column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60) (Office Action at page 3).

However, Tomalia et al. actually teaches a compound with the formula $(T)_e*(P)_x*(M)_y$ (column 16, lines 37-52), (column 18, lines 23-67), (column 19, lines 1-67), (column 20, lines 1-29), (column 22, lines 20-26), wherein M represents a diagnostic or therapeutic agent, such as a radionuclide, T represents a target director, such as a moiety that can bind a cell-surface molecule, or a PNA that can bind a nucleic acid, P represents a dendrimer, and wherein M and T

are associated with P via identical or different bonds, *. However, the instant application discloses a compound X-L1-P-L2-T, wherein X represents a diagnostic or therapeutic agent, such as a radionuclide chelated to a dendrimer (comparable to P*M in Tomalia et al.), P represents a PNA that can bind a nucleic acid (comparable to T in Tomalia et al.), and T represents a cell surface target director, such as a moiety that can bind a cell-surface molecule (comparable to T in Tomalia et al.), and wherein X, P and T are associated with identical or different spacers L1 and L2 to prevent steric hindrance. The L1 and L2 spacers are a non-obvious solution, not taught by Tomalia et al., to the problem of steric hindrance between the three functional units of the claimed compound.

The Examiner argues that Tomalia et al. teach that two or more dendrimers can be associated with each other (covalently bridged or through other associations, citing claim 12 of the '166 patent) (Office Action at page 3). However, Tomalia et al. discloses that (column 17, lies 41-67):

> As used herein, "associated with" means that the carried material(s) can be physically encapsulated or entrapped within the core of the dendrimer, dispersed partially or fully throughout the dendrimer, or attached or linked to the dendrimer or any combination thereof, whereby the attachment or linkage is by means of covalent bonding, hydrogen bonding, adsorption, absorption, metallic bonding, van der Waals forces or ionic bonding, or any combination thereof.

While this section of the Tomalia specification comprises a general statement listing all envisioned kinds of bonding, Tomalia et al. specifically restricted "genetic materials" (which include PNA) as belonging to a class for which "formation of the complex does not take place via covalent bonding" ('166 Tomalia at column 47, lines 55-62). The other recitations of the

$(T)_e*(P)_x*(M)_y$ structure ('166 Tomalia at column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60) do not teach that M represents a PNA. At no point in patent 5,714,166 do Tomalia et al. state that PNA, or any genetic material, can be covalently bonded to a dendrimer, not in the claims, not in the background, not in the examples. Therefore, Tomalia et al. teach away from covalent bonding of genetic materials to dendrimers.

In addition, the order of functional units in the claimed compound X-L1-P-L2-T (comparable to M*L0*P*L1*T1*L2*T2 in Tomalia et al.), is vital to the purpose of entering a cell, then binding to a nucleic acid target. The compound $(T)_e*(P)_x*(M)_y$ taught by Tomalia et al. permits compound binding to multiple neighboring cells via multiple T2 interactions on the surface of the dendrimer P, preventing internalization of the compound into a single targeted cell, which in turn will prevent T1 binding to the targeted nucleic acid inside the cell.

The Examiner further argues that Tomalia et al. teach a compound with the formula T-L1-P-L2-M, wherein P and M are the equivalents of X and P of the instant claims, i.e., that they teach a compound with the formula T-L1-X-L2-P and that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property (Office Action at page 5). The Examiner alleges that the arrangement is not significant if it does not provide a novel feature, and that it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site (Office Action at page 5).

However, Applicant has attempted to utilize the PAMAM dendrimer designed by Donald Tomalia, despite the teaching of the Tomalia patent that genetic material was never covalently bonded to PAMAM, as set forth on the Declaration under 37 CFR 1.132 of Dr. Eric Wickstrom, filed herewith.

As set forth on the Declaration (paragraphs 8-12), the attempt to produce this construct failed. The federal Circuit has held that if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) MPEP 2143.01. Here, the Examiner attempts to argue that Tomalia can be modified with the Meade and Basu patent to teach or suggest the claimed invention, however, this modification would be unsatisfactory for its intended purpose, as demonstrated by the unsuccessful attempt by Applicant to synthesize a functional compound as claimed using the teachings or suggestions of Tomalia.

In fact, Applicant had to completely alter the approach to synthesize the instantly claimed compound (Declaration at paragraphs 13-17). Here, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. See In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959), in which the court reversed a rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate."

270 F.2d at 813, 123 USPQ at 352.). MPEP 2143.01.

Here, the Examiner argues that the primary reference (the Tomalia patent) can be modified to teach or suggest all components necessary for the arrangement as set forth in the claims. However, attempting to use the teachings of Tomalia to reach the claimed invention was unsuccessful, thereby showing that it would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate, as in the In re Ratti case.

In addition, while obviousness does not require absolute predictability, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness, see In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) MPEP 2143.02. Here, Applicants attempt to use the Tomalia teachings as the basis for to reach the claimed invention was unsuccessful, thereby showing that there was no reasonable expectation of success in modifying the Tomalia teachings.

Therefore, the evidence provided by Applicant demonstrates that Applicant has attempted to utilize the PAMAM dendrimer according to the teachings of Tomalia, and that this attempt was unsuccessful.

There is no suggestion in the Tomalia et al. reference to modify its teaching to yield the present invention. Therefore, the Tomalia et al. reference would not have motivated one of ordinary skill in the art to reach the claimed invention when it teaches that genetic material can be complexed with a dendrimer only via a non-covalent association (see Tomalia at col. 47, lines 55-62). Following this reference, one of ordinary skill in the art would have lacked motivation

to use its teachings alone or in combination with the teachings of the secondary reference to make the composition of the present invention with a reasonable expectation of success. Absent such reasonable motivation, there can be no *prima facie* case of obviousness. See, e.g., MPEP § 2143.

The Examiner admits that Tomalia et al. do not teach a biodegradation cleavage site, but argues that Meade et al. teach a biodegradation cleavage site (claim 11) (column 14, lines 20-30). The Examiner further argues that with respect to the limitation recited in claim 28, PNAs comprise N-aminoethylglycine backbone units and the bases are covalently bound to the backbone by methylene-carbonyl units (see Basu et al.).

However, the secondary references Meade and Basu do not remedy the aforementioned deficiency of the primary reference, the Tomalia et al. patent, to teach or suggest all the limitations of the claims because Meade et al. do not disclose utilizing PNA covalently bound to a dendrimer and or targeting messenger RNA in a cell. Moreover, it would not be obvious to a person skilled in the art to modify the teachings of Tomalia with Meade and Basu to reach all the limitations of the claims, for the reasons set forth in the Declaration of Dr. Eric Wickstrom. Therefore, all the limitations of the claims are not taught or suggested ion the combination of the Tomalia, Meade, and Basu references.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 86, and 88-92 under 35 U.S.C. 103(a) is respectfully requested.

* * *

Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48, 49-52, 54-56, 69-73, 75, 80, 82, 83, 86, and 88-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., taken with both Meade et al. and Basu et al., in further view of Nakano et al. This rejection is respectfully traversed.

The Examiner admits that Tomalia et al., Meade et al., and Basu et al. do not teach an oncogene, wherein the oncogene is KRAS (claims 32, 33, 72, and 82), nor do they specifically teach treating pancreatic cancer (claim 49), but argues that Nakano et al. teach gene therapy by using antisense KRAS as a therapeutic agent for cancer (Abstract, p. 492, column 1, last paragraph, p. 493 bridging p. 495). The Examiner alleges that it would have been obvious to one of skill in the art, at the time the invention was made, to use the compound and the method of Tomalia et al., Meade et at., and Basu et al., wherein the PNA is directed against KRAS, to deliver diagnostic and therapeutic agents to cancer cells such as colon and pancreatic cancer cells that are known to over-express KRAS, with a reasonable expectation of success:

However, the Tomalia, Meade and Basu references were addressed above, and the addition of the Nakano et al. reference does not cure the deficiency of the combined references to teach or suggest all the limitations of the claims because Nakano, et al. teach multiple intratumoral injections of an adenovirus that overexpresses 347 nucleotides of KRAS RNA to lower translation of KRAS mRNA and slow the growth of colorectal cancer xenografts in mice, as opposed to the compounds comprising targeting moieties as in the instant claims. Further, Nakano, et al. do not teach probes (short oligonucleotide less than 20 nucleotides) binding to specific receptors on cells, probe internalization into cells via receptor, probe release into cellular

cytoplasm, or probe binding to mRNA in cellular cytoplasm. Therefore, all the limitations of the claims are not taught or suggested in the combination of the Tomalia, Meade, Basu, and Nakano references.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48, 49-52, 54-56, 69-73, 75, 80, 82, 83, 86, and 88-92 under 35 U.S.C. 103(a) is respectfully requested.

* * *

Claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, and 89-92 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (Bioconjugate Chem, 2002, 13: 11 76-1 1 80), in view of both Liang et al. and Basu et al. This rejection is respectfully traversed.

Lewis et al. teach a DOTA-PNA conjugate designed to target oncogene BCL2 mRNA, wherein DOTA comprises a radiometal (i.e., a polymeric diagnostic moiety) and wherein the PNA, which is 18 bases long, is further coupled to a peptide designated for intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety); the targeting peptide and DOTA are conjugated to PNA via linkers. Lewis et al. teach contacting cells known to comprise high and low levels of BCL2 expression with the DOTA-PNA peptide conjugate, allowing for the conjugate to be internalized by the cells, and detecting the conjugate within the cells to determine the level of expression of BCL2 transcript

The Examiner argues that while Lewis et al. does not teach the specific arrangement recited in the instant claims, i.e., X-L1-P-L2-T, that Lewis et al. teaches all components

necessary for this arrangement. The Examiner argues that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property, and that the arrangement is not significant if it does not provide a novel feature. The Examiner alleges that it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site.

However, the Lewis et al. reference does not teach or suggest each and every element recited in the claims because it does not disclose a conjugate comprising "a targeting moiety that is capable of binding to a cell surface molecule or being bound by a cell surface molecule" which is covalently linked to PNA. On page 7 of the Office Action, the Examiner stated that

> Lewis et al. teach a DOTA-PNA conjugate designed to target *bcl-2* (i.e., an oncogene), wherein DOTA comprises a radiometal (i.e., a polymeric diagnostic moiety) and wherein the PNA, which is 18 bases long, is further coupled to a peptide designated for intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety); the targeting peptide and DOTA are conjugated to PNA via linkers (Abstract, p. 1177, Fig. 1). Lewis et al. teach contacting cells known to comprise high and low levels of *bcl-2* with the DOTA-PNA-peptide conjugate, allowing for the conjugate to be internalized by the cells, and detecting the conjugate within the cells to determine the level of expression of *bcl-2* transcript (emphasis added).

The Examiner improperly equates a peptide designated for universal intracellular delivery of the radiolabeled PNA (i.e., a membrane permeating peptide PTD-4) with a specific targeting moiety of the present invention, which is defined in the specification on page 21, lines 20-21 as "a moiety that "comprises any chemical substance that is capable of binding to a cell surface molecule or being bound by a cell surface molecule (e.g., a receptor)." Targeting the conjugate

of the invention to a cell surface receptor so that the internalization is achieved via a receptor provides the desired specificity. This specificity cannot be achieved when a general membrane permeating peptide is used instead of a particular cell surface receptor. Therefore, the membrane permeating peptide as described in Lewis et al. does not constitute a "targeting moiety" contemplated in this invention. Consequently, the Lewis et al. reference does not teach or suggest the invention because it does not identically disclose each and every element recited in the claims.

As evidence of this, Sun et al. (Sun et al. MicroPET imaging of MCF-7 tumors in mice via unr mRNA-targeted peptide nucleic acids. *Bioconjug Chem.* Mar-Apr 2005;16(2):294-305, previously cited on the IDS of 5-14-2007), reported an attempt to image *UNR* mRNA in human MCF7 xenografts using DO3A-Tyr-PNA-Lys_4 conjugates, a structure used previously by Lewis, et al. However, sequence-specific tumor images were not reliably observed. The four-lysine tail at the carboxy terminus of the conjugates enabled universal cell permeation. The lack of specific tumor contrast was ascribed by Sun et al. to uptake of the [^{64}Cu]PNA-Lys_4 conjugates into all cells, so that murine *unr* mRNA with the same target sequence as human *UNR* mRNA might have contributed to PET image intensities in all tissues (see Sun at page 302, column 2).

In addition, newly added claims 93-95 recite that the diagnostic or therapeutic moiety is separated from the PNA by a distance of from about 10A to about 30A by one or more linking moieties. In contrast, the Lewis reference teaches direct bonding of the non-specific peptide and a radionuclide-containing moiety to the PNA. This is in contrast to the instantly claimed compounds, in which linking moieties are used to connect the targeting sequence and treatment

moieties to the PNA. In addition, new claims 93-95 recite that the linking moieties are 10A to 30A. This is in contrast to the Lewis compound, in which the moieties are directly linked to the PNA. Thus Lewis does not teach or suggest all the limitations of the claims. These deficiencies are not addressed by the Liang et al reference.

While the Examiner acknowledged that Lewis et al. "do not teach a targeting moiety capable of binding to a cell surface molecule (claim 1)" (Office Action at pages 7 and 8), the Examiner cites the Liang et al. reference to allegedly remedy the deficiency of Lewis et al. to teach the targeting moiety. Liang et al. teach construction of a transferrin-PNA conjugate associated with a plasmid DNA vector for the purpose of plasmid DNA vector delivery into cells to effect gene therapy. It is important to note that Liang et al. reported no cellular uptake of the transferrin-PNA:DNA conjugate until cationic polymer polyethyleneimine, associated with a plasmid DNA vector was added (see Liang at page 240, Figure 5 and Figure 6). Liang et al. reported enhanced vector-encoded enzymatic activity in transfected cells if transferrin-PNA was associated with the plasmid DNA vector:polyethyleneimine complex. Therefore Liang et al. provide no motivation toward the design of the present diagnostic compound without the concurrent use of polyethyleneimine.

The toxicity of polyethyleneimine, however, teaches away from utilizing the Liang et al. construct. The toxicity of polyethyleneimine is taught in Ochietti et al. (Ochietti B et al., Inducing neutrophil recruitment in the liver of ICAM-1-deficient mice using polyethyleneimine grafted with Pluronic P123 as an organ-specific carrier for transgenic ICAM-1. Gene Ther. 2002 Jul;9(14):939-45) which teaches (Ochietti at page 941):

Polyethyleneimine (PEI) is a cationic polymer that provides effective gene

> expression in many in vitro settings and in vivo, when administered locally. However, similarly to cationic liposomes, PEI-DNA complexes tend to spontaneously aggregate and accumulate in lungs upon systemic administration, which often leads to microembolisms in capillaries and related acute toxicity, and also significantly reduces bioavailability of DNA to tissues other than lung. In addition, strong hemolytic toxicity of PEI and some other cationic polymers have been reported as a dose-limiting factor for their systemic administration.

Additionally, the construct of Liang et al. lacks the specificity provided by the present invention. Transferrin is so large, its binding to its receptor is so strong, and the transferrin receptor is so ubiquitous, that all cells would take up transferrin and any other moiety conjugated to it, regardless of the presence or absence of the target nucleic acid in a cell.

Indeed, while Liang et al. provided no control experiment with PNA conjugated to any other protein, others compared transferrin-drug conjugates with albumin-drug conjugates. Albumin is another large, ubiquitous protein found in blood at high concentration, providing no specificity to cancer cells. Transferrin and albumin function as formulation agents, then, rather than specificity agents. The equivalence of transferrin and albumin is taught in Kratz et al. (Kratz F et al., In vitro and in vivo efficacy of acid-sensitive transferrin and albumin doxorubicin conjugates in a human xenograft panel and in the MDA-MB-435 mamma carcinoma model. J Drug Targeting. 2000 May;8(5):305-18) which teaches (see Abstract):

> Subsequently, the efficacy of an acid-sensitive transferrin and albumin doxorubicin conjugate, which both incorporated a phenylacetyl hydrazone bond as a predetermined breaking point, was evaluated in the xenograft mamma carcinoma model MDA-MB-435 in comparison to free doxorubicin (dose, i.v.: 2 x 4, 8 and 12 mg/kg). The conjugates showed significantly reduced toxicity (reduced lethality and body weight loss) with a concomitantly stable or slightly improved antitumour activity compared to free doxorubicin...Interestingly, there is no pronounced difference between identically constructed transferrin and albumin doxorubicin conjugates with regard to in vitro or in vivo efficacy.

Therefore, all the limitations of the claims are not taught or suggested by the combination of the Lewis, Liang and Basu references.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, and 89-92 under 35 U.S.C. 103(a) is respectfully requested.

* * *

Claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 75, 80, 82, 83, 86, and 89-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., in further view of Nakano et al. This rejection is respectfully traversed.

The Examiner argues that Lewis et al., Liang et al., and Basu et al. do not teach or suggest KRAS (claims 33 and 82), but alleges that Nakano et al. teach gene transfer antisense KRAS as a therapeutic agent for cancer (Abstract, p. 492, column 1, last paragraph, p. 493 bridging p. 495) and that it would have been obvious to one of skill in the art, at the time the invention was made, to modify the compound of Lewis et al., Liang et al., and Basu et al. by using a PNA directed against KRAS and use it in a method of delivering diagnostic and therapeutic agents to cancer cells over-expressing KRAS, such as colon and pancreatic cancer cells, with a reasonable expectation of success

However, the Lewis, Liang, and Basu references were addressed above, and the addition of the Nakano et al. reference does not cure the deficiency of the combined references to teach or suggest all the limitations of the claims because Nakano, et al. teach multiple intratumoral

injections of an adenovirus that overexpresses 347 nucleotides of KRAS RNA to lower translation of KRAS mRNA and slow the growth of colorectal cancer xenografts in mice, as opposed to the compounds comprising targeting moieties as in the instant claims. Further, Nakano, et al. do not teach probes (short oligonucleotide less than 20 nucleotides) binding to specific receptors on cells, probe internalization into cells via receptor, probe release into cellular cytoplasm, or probe binding to mRNA in cellular cytoplasm. Therefore, all the limitations of the claims are not taught or suggested in the combination of the Lewis, Liang, Basu, and Nakano references.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 75, 80, 82, 83, 86, and 89-92 under 35 U.S.C. 103(a) is respectfully requested.

* * *

Claims 1, 3, 4, 7-14, 16, 26-32, 34, 41-45, 48-52, 54-56, 69-73, 80, 83, 86, and 88-92 are rejected under 35 U.S.C.. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., in further view of both Tomalia et al. and Meade et al. This rejection is respectfully traversed.

The Examiner admits that Lewis et al., Liang et al., and Basu et al. do not teach a dendrimer or a plurality of chelants optionally complexed to one or more diagnostic metal ions, a biodegradation cleavage site, or intravascular administration (claims 7-14, 16, 26, 27, 43-45, 54-56, and 88), but argues that Tomalia et al. and Meade et al. teach these limitations, and that it would have been obvious to one of skill in the art, at the time the invention was made, to modify

the method of Lewis et al., Liang et al., and Basu et al. according to the teachings of Tomalia et al. and Meade et al., with a reasonable expectation of success.

However, as discussed above, the Lewis, Liang and Basu references do not teach or suggest a conjugate comprising "a targeting moiety that is capable of binding to a cell surface molecule or being bound by a cell surface molecule" which is covalently linked to PNA, and this deficiency is not cured by the Tomalia or Meade patents, because, as set forth above, as evidenced by the Declaration of Dr. Eric Wickstrom, attempting to use the teachings of Tomalia to reach the claimed invention was unsuccessful, thereby showing that it would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate, and Meade et al. does not disclose utilizing PNA covalently bound to a dendrimer and or targeting messenger RNA in a cell. Therefore, all the limitations of the claims are not taught or suggested in the combination of the Lewis, Liang, Basu, Tomalia, and Meade references.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3, 4, 7-14, 16, 26-32, 34, 41-45, 48-52, 54-56, 69-73, 80, 83, 86, and 88-92 under 35 U.S.C. 103(a) is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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December 19, 2007

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.